(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 315 964 B1**

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **07.01.93**

(51) Int. Cl.[5]: **A61K 31/12**, A61K 47/38

(21) Application number: **88118627.4**

(22) Date of filing: **09.11.88**

(54) A novel pharmaceutical composition comprising exifone and water-soluble polymer.

(30) Priority: **11.11.87 JP 284493/87**

(43) Date of publication of application:
17.05.89 Bulletin 89/20

(45) Publication of the grant of the patent:
07.01.93 Bulletin 93/01

(84) Designated Contracting States:
AT BE CH DE ES FR GB IT LI LU NL SE

(56) References cited:
EP-A- 0 137 198
EP-A- 0 240 773
DE-A- 1 492 034
FR-A- 2 257 272
FR-A- 2 377 202

(73) Proprietor: **Laboratoires Pharmascience**
73, blvd. de la Mission Marchand
F-92400 Courbevoie(FR)

(72) Inventor: **Ueda, Yoshio**
3-5-204, Mikagenakamachi 1-chome
Higashinada-ku
Kobe-shi Hyogo 658(JP)
Inventor: **Shimojo, Fumio**
2-13, Daiwahigashi 2-chome Kawanishi-shi
Hyogo 666-01(JP)
Inventor: **Yasumura, Mitsuru**
37, Matsuzonocho 5-chome
Nishinomiya-shi Hyogo 662(JP)
Inventor: **Toyoshima, Kenzo**
1327, Tanidacho
Ikoma-shi Ikoma-shi Nara 630-02(JP)
Inventor: **Nakahashi, Nobumitsu**
12-3, Hamamachi Kadoma-shi
Osaka 571(JP)

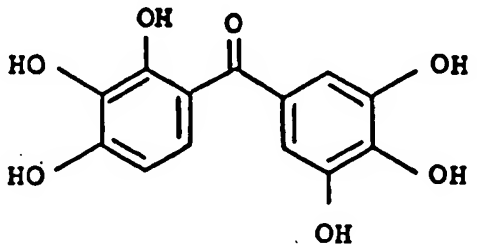
(74) Representative: **Martin, Jean-Jacques et al**
Cabinet REGIMBEAU Martin, Schrimpf, Warcoin, Ahner 26, Avenue Kléber
F-75116 Paris(FR)

EP 0 315 964 B1

Description

The present invention relates to a novel pharmaceutical composition comprising a physical mixture comprising exifone and a water-soluble cellulose derivative, which improves low absorbability of exifone upon oral administration, and so is useful in the pharmaceutical field.

Exifone, which has the structure shown below, is useful as a cerebral metabolic improving agent and effective, for example, in the treatment of senile dementia, and cerebrovascular dementia.



[2,3,4,3',4',5'-Hexahydroxybenzophenone]

For example, a pharmaceutical composition for the treatment of functional deficiencies and metabolic irregularities resulting from cerebral and/or peripheral circulatory deficiency which comprises as active ingredient exifone in admixture with the pharmaceutically suitable carrier is described in FR-A-2377202.

However, exifone is sparingly soluble in water (saturated solubility : about 70-80 μg/ml) and has disadvantage that when it is orally administered as a conventional pharmaceutical composition, its absorption into blood circulation is poor and accordingly its bioavailability is low. Therefore, the advent of a novel pharmaceutical composition which can overcome this drawback has been awaited.

The inventors of the present invention found that the above drawback can be overcome by compounding exifone and a water-soluble cellulose derivative, and as a result of our intensive investigations, we have completed the present invention.

The present invention is the first that has overcome the above drawback of exifone.

The novel pharmaceutical composition of the present invention is characterized in that it comprises a physical mixture comprising exifone and a water-soluble cellulose derivative. By the coexistence of exifone and a water-soluble cellulose derivative the drawback that exifone is sparingly soluble in water is improved and high bioavailability can be attained upon oral administration.

The pharmaceutical composition of the present invention may further contain, if necessary, conventional additive(s) used ordinarily in the process of making up pharmaceutical compositions, such as disintegrants, lubricants, excipients and colorants. The dosage form is not critical, thus, upon oral administration, the composition can be used, as desired, in the form of powders, fine granules, granules, capsules, tablets and film-coated tablets.

Suitable examples of the water-soluble cellulose derivative to be used in this pharmaceutical composition are those ordinarily used in this field of the art, such as, hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose. Among these, the more preferred cellulose derivatives may be hydroxypropylmethylcellulose and hydroxypropylcellulose.

Suitable disintegrants may include, for example, starch species (e.g. potato starch, corn starch, hydroxypropylstarch, carboxymethylstarch sodium,), cellulose derivatives (e.g. carboxymethylcellulose calcium, carboxymethylcellulose, low substituted hydroxypropylcellulose). Suitable lubricants may include, for example, talc, wax species (e.g. white beeswax, hardened oils,), stearic acid species (e.g. stearic acid, magnesium stearate, calcium stearate,). Suitable excipients may include, for example, sugars (e.g. lactose, sucrose,), starch species (e.g. corn starch,), cellulose derivatives (e.g. microcrystalline cellulose,), inorganic calcium salts (e.g. calcium hydrogen phosphate, calcium sulfate,) and suitable colorants may include, for example, tar dyes.

The pharmaceutical composition of the present invention which comprises a physical mixture comprising exifone and a water-soluble cellulose derivative can be produced by compounding exifone and the above-mentioned water-soluble cellulose derivative, if necessary, together with the above-mentioned conventional additive(s), and then converting the mixture to a desired dosage form.

The process for the preparation of the pharmaceutical composition of the present invention by

compounding exifone and water-soluble cellulose derivative is the process to mix these substances, and the process is described in detail hereinbelow.

Process to mix the substances

The pharmaceutical composition of the present invention can be produced by mixing exifone with a water-soluble cellulose derivative, if necessary, together with a conventional additive(s).

The means of mixing to be used in this process may be any means conventionally employed in this field of the art. For further decreasing the particle size, the resulting mixture may be milled. The milling can be performed by a conventional method.

The thus-produced mixture comprising a physical mixture comprising exifone and a water-soluble cellulose derivative, if desired, can be converted to various dosage forms by the steps conventionally used in this field of the art, for example, milling sieving, kneading, granulating, tableting and coating. These steps may be carried out in the conventional manner.

This process, Process to mix the substances, is suitable for industrial production because of its being easy to perform.

In producing the pharmaceutical composition of the present invention by this process, it is particularly preferable to knead the mixed powder with a suitable kneading solvent and then convert the kneaded matter to the desired dosage form. Suitable kneading solvents may include water, ethanol, and mixtures thereof.

The pharmaceutical composition of the present invention which comprises exifone and a can be produced by the above-mentioned process. In its production, the kind and the amount of the water-soluble cellulose derivative and additive(s) to be used can be selected suitable depending, for example, upon the desired dosage form, the content of exifone therein, the desired dissolution pattern of exifone, and so forth.

The compounding ratio of exifone and the cellulose derivative is preferably about 1:0.01 to about 1:7 by weight, more preferably 1:0.05 to 1:5 by weight.

In the following, the present invention is explained in detail by Examples.

(I) Process to mix the substances

Example 1

Exifone (10 g) was placed, together with TC-5R (5 g)(trademark, product of Shin-Etsu Chemical; generic name; hydroxypropylmethylcellulose) and Explotab (2.5 g) (trademark; product of Kimura Sangyo; generic name: carboxymethylstarch sodium) in a polyethylene bag, and the contents were mixed by shaking it well to give a mixed powder comprising TC-5R-treated exifone.

Example 2

Exifone (10 g) and TC-5R (5 g) were placed in a polyethylene bag, and the contents were mixed by shaking it well, then the mixture was milled in a coffee mill for 5 minutes. Explotab (2.5 g) was added to the milled mixture, and the whole was placed in a polyethylene bag and mixed by shaking it well to give a mixed powder comprising TC-5R-treated exifone.

Example 3

After exifone (10 g) and TC-5R (0.5 g) were mixed together in a beaker, the resulting mixture was then kneaded with a 20% agueous ethanol solution (4 ml) and granulated. After dried in vacuo, the granules were milled in a mortar to an appropriate size and filled into No. 0 capsules to give a capsulated composition.

The formulation per one capsule was as follows :

Exifone	200 mg
TC-5R	10 mg
	210 mg

Example 4

A capsulated composition having the following formulation was produced from exifone (10 g) and HPC-L (0.5 g) (trademark; product of Nippon Soda; generic name : hydroxypropylcellulose) according to a similar manner to that of Example 3 :

Exifone	200 mg
HPC-L	10 mg
	210 mg

Example 5

Exifone (10 g) was mixed with TC-5R (1.5 g) in a beaker, and then the mixture was kneaded with a 20% aqueous ethanol solution (5 ml) and granulated. After dried in vacuo, the granules were milled in a mortar and then placed with Explotab (0.35 g) in a polyethylene bag and the mixture was mixed by shaking the bag well to give a TC-5R-treated powder. This mixed powder was filled into No. 0 capsules to give a capsulated composition, each capsule having the following formulation :

Exifone	200 mg
TC-5R	30 mg
Explotab	7 mg
	237 mg

Example 6

To the mixed powder comprising TC-5R-treated exifone as obtained according to a similar manner to that of Example 11 was added magnesium stearate (0.15 g) and tabletted by a single punch tabletting machine to give tablets, each having the following formulation :

Exifone	200 mg
TC-5R	30 mg
Explotab	7 mg
Magnesium stearate	3 mg
	240 mg

Example 7

A capsulated composition was produced from exifone (10 g) and TC-5R (2.5 g) according to a similar manner to that of Example 9, each capsule having the following formulation :

Exifone	200 mg
TC-5R	50 mg
	250 mg

Example 8

A capsulated composition was produced from exifone (10 g), TC-5R (2.5 g) and Explotab (2.5 g) according to a similar manner to that of Example 5, each capsule having the following formulation :

Exifone	200 mg
TC-5R	50 mg
Explotab	50 mg
	300 mg

Example 9

A capsulated composition was produced from exifone (10 g), TC-5R (5 g) and Explotab (2.5 g) according to a similar manner to that of Example 5, each capsule having the following formulation :

Exifone	200 mg
TC-5R	100 mg
Explotab	50 mg
	350 mg

Example 10

A capsulated composition was produced from exifone (10 g), TC-5R (10 g) and Explotab (5 g) according to a similar manner to that of Example 5, each capsule having the following formulation :

Exifone	100 mg
TC-5R	100 mg
Explotab	50 mg
	250 mg

Example 11

A capsulated composition was produced from exifone (10 g), TC-5R (30 g) and Explotab (20 g) according to a similar manner to that of Example 5, each capsule having the following formulation :

Exifone	50 mg
TC-5R	150 mg
Explotab	100 mg
	300 mg

Example 12

A capsulated composition was produced from exifone (10 g), TC-5R (50 g) and Explotab (20 g) according to a similar manner to that of Example 5, each capsule having the following formulation :

Exifone	50 mg
TC-5R	250 mg
Explotab	100 mg
	400 mg

Example 13

Exifone (200 g) and TC-5R (100 g) were mixed with each other by shaking well in a polyethylene bag, the mixture was then kneaded with a 20% aqueous ethanol solution (80 ml) as a kneading solvent and granulated using a Planetary mixer for kneading. The granules obtained were dried at 40 °C in vacuo and then milled using Tornado type mill (20 mesh). The powder obtained was mixed with Explotab (27 g) in a polyethylene bag, and the resulting mixture was filled into No. 0 capsules to give a capsulated composition, each having the following formulation :

Exifone	200 mg
TC-5R	100 mg
Explotab	27 mg
	327 mg

Examples 14

(1) To the TC-5R-treated powder (before filling into capsules) obtained in Example 13 was added Explotab, Avicel (trademark; product of Asahi Chemical Industry; generic name : microcrystallinecellulose) and magnesium stearate, and then the mixture was tableted in the conventional manner to give tablets each having the following formulation :

Exifone	200 mg
TC-5R	100 mg
Explotab	37 mg
Avicel	20 mg
Magnesium stearate	3 mg
	360 mg

(2) The above tablets were film-coated by a conventional method to give film-coated tablets. The formulation of film coat layer per tablet was as follows :

TC-5R	5.4 mg
Polyethylene glycol 6000	0.8 mg
Titanium oxide	1.7 mg
Yellow iron sesquioxide	0.1 mg
	8.0 mg

Example 15

Exifone (750 g), TC-5R (375 g), Explotab (101.25 g), lactose (678.75 g) and avicel (678.75 g) were mixed, granulated with an aqueous solution of citric acid (18.75 g), dried and sieved in a conventional method to give granules (2540 g). The granules obtained were mixed with magnesium stearate (33.08 g) and then tabletted in a conventional manner. The tablets thus obtained were film-coated in a conventional method to give film-coated tablets, each having the following formulation :

Core Tablet	
Exifone	40 mg
TC-5R	20 mg
Explotab	5.4 mg
citric acid	1 mg
lactose	35.6 mg
Avicel	36.2 mg
magnesium stearate	1.8 mg
	140 mg

Film Coat Layer	
TC-5R	3.8 mg
Polyethylene glycol 6000	0.5 mg
titanium oxide	0.56 mg
yellow ferric oxide	0.14 mg
carnauba wax	trace
	5 mg

In the pharmaceutical composition of the present invention the solubility of exifone was markedly improved as compared with the exifone bulk substance and, when orally administered, a sufficient bioavailability can be obtained.

In the following, for demonstrating the above fact, we set forth the dissolution test results and absorption test results (in dogs) obtained with several representative pharmaceutical compositions produced in accordance with the present invention.

Dissolution test 1

[I] Compostion tested

Composition A : The mixed powder comprising TC-5R-treated exifone obtained in Example 1 (exifone : TC-5R = 1:0.5)

Composition B : The capsule containing a mixed powder comprising TC-5R-treated exifone obtained in Example 3 (exifone : TC-5R = 1:0.05)

Composition C : The capsule containing a mixed powder comprising HPC-L-treated exifone obtained in Example 4 (exifone:HPC-L = 1:0.05)

Composition D : The tablet comprising a mixed powder comprising TC-5R-treated exifone obtained in Example 6 (exifone : TC-5R = 1:0.15)

Composition E : The capsule containing a mixed powder comprising TC-5R-treated exifone obtained in Example 7 (exifone : TC-5R = 1:0.25)

Composition F : The capsule containing a mixed powder comprising TC-5R-treated exifone obtained in Example 9 (exifone : TC-5R = 1:0.5)

Control composition : The same control composition as used in Dissolution test 1.

[II] Test method

The dissolution percent was determined with passage of the time by the dissolution test method (2nd method) prescribed in the 11th edition of The Pharmacopoeia of Japan. The test conditions were as follows :

Dissolution tester	Toyama Sangyo model
Sample quantity	200 mg as exifone
Test solution and its quantity	1st fluid (pH 1.2), 900 ml
Paddle speed	100 rpm
Measurement	uv wavelength 385 nm

[III] Test results

The dissolution percent obtained at each measurement time was as follows :

Time (minutes) / Test composition	30	60
Composition A	52.1	68.1
Composition B	78.4	83.1
Composition C	68.3	71.7
Composition D	85.8	88.6
Composition E	80.2	93.8
Composition F	81.6	84.9
Control composition	11.4	12.4

The above test results show that in the pharmaceutical compositions of the present invention as produced by the process to mix the substances, whether in the form of mere mixtures or in any of the various dosage forms derived therefrom and in any of the varied mixing ratios, their dissolution patterns were markedly improved as compared with the exifone bulk substance and that, therefore, the drawback of exifone, its sparing solubility, has been markedly improved.

Since it has been so far believed that mere mixing of a sparingly soluble medicinal substance with a water-soluble cellulose derivative can hardly be expected to result in an improved solubility, the finding that mere mixing may produce a marked improvement as in the pharmaceutical composition of the present invention may be said to be a quite unexpected one.

Dissolution test 2

[I] Compositions tested

Composition G : The capsule containing a mixed powder comprising TC-5R-treated exifone obtained in Example 13 (exifone : TC-5R = 1:0.5)

Composition H : The film-coated tablet comprising a mixed powder comprising TC-5R-treated

exifone obtained in Example 15 (exifone : TC-5R = 1:0.5)

Control composition : The same control composition as used in Dissolution test 1.

[II] Test method

The same method as used in Dissolution test 1 was used.

[III] Test results

The dissolution percent obtained at each measurement time was as follows :

Test composition \ Time (minutes)	5	15	30	60	120
Composition G	33.1	60.5	70.8	72.9	81.7
Composition H	13.4	61.8	74.5	79.1	79.1
Control composition	10.4	10.5	11.4	12.4	16.0

For demonstrating that an improvement in dissolution behavior can lead to an improvement in absorption upon oral administration, an absorption tests were performed in dogs using the representative pharmaceutical compositions of the present invention. The results are shown below.

Absorption test 1

[I] Compositions tested

Composition G and Control composition, as used in Dissolution test 2 were used.

[II] Test method

The absorption test was performed in six male beagle dogs (weighing 9.0-11.5 kg; fasted from the previous day) by the three-way cross-over method.

The dose was 200 mg as exifone per dog (1 capsule of each test composition) and the test compositions were administered orally. After administration, blood samples were taken from the antebrachial vein with passage of the time and immediately assayed for exifone by the HPLC method.

[III] Test results

Plasma concentrations at each measurement time after oral administration, maximum plasma concentrations (C_{max}),times required for the plasma concentration to reach a maximum (T_{max}), and areas under the plasma concentration-time curve (AUC_{0-6}) are shown in the following table.
Each data is given in terms of "mean ± standard error".

Test composition \ Time	Plasma concentration (μg/ml)						
	15 min	30 min	60 min	120 min	180 min	240 min	360 min
Composition 6	0.99 ±0.45	1.28 ±0.22	0.96 ±0.13	0.54 ±0.12	0.19 ±0.06	0.18 ±0.06	0.15 ±0.07
Control composition	0.07 ±0.05	0.15 ±0.07	0.14 ±0.06	0.20 ±0.07	0.11 ±0.07	0.07 ±0.07	0.10 ±0.10

Test compound	C_{max} (μg/ml)	T_{max} (hr)	AUC_{0-6} (μg·hr/ml)
Composition 6	1.50 ±0.36	0.50 ±0.11	2.59 ±0.41
Control composition	0.30 ±0.06	1.58 ±0.58	0.69 ±0.17

Absorption test 2

[I] Compositions tested

Composition G and Composition H as used in Dissolution test 2 were used.

[II] Test method

The absorption test was performed in six male beagle dogs (weighing 9.0-11.5 kg; fasted from the previous day) by the two-way cross-over method.

The dose was 200 mg as exifone per dog (1 capsule of Composition G and 5 tablets of Composition H) and the test composition were administered orally. After administration, blood samples were taken from the antebrachial vein with passage of the time and immediately assayed for exifone by the HPLC method.

[III] Test results

Plasma concentrations at each measurement time after oral administration, maximum plasma concentrations (C_{max}),times required for the plasma concentration to reach a maximum (T_{max}), and areas under the plasma concentration-time curve (AUC_{0-8}) are shown in the following table.
Each data is given in terms of "mean ± standard error".

Time / Test composition	Plasma concentration (μg/ml)							
	15 min	30 min	60 min	120 min	180 min	240 min	360 min	480 min
Composition G	0.50 ±0.75	1.20 ±0.70	1.01 ±0.36	0.56 ±0.34	0.42 ±0.43	0.38 ±0.46	0.15 ±0.07	0.13 ±0.08
Composition H	0.74 ±0.84	1.47 ±0.37	0.96 ±0.06	0.47 ±0.28	0.20 ±0.05	0.16 ±0.07	0.14 ±0.04	0.13 ±0.05

Test compound	C_{max} (μg/ml)	T_{max} (hr)	AUC_{0-8} (μg·hr/ml)
Composition G	1.52 ±0.39	1.33 ±1.35	3.34 ±0.88
Composition H	1.66 ±0.34	0.50 ±0.15	2.78 ±0.42

The above test results clearly show that, as expected on the basis of the results of Dissolution test 2, in the pharmaceutical compositions of the present invention, obtained by the process to mix the substances, the absorbability into the blood circulation were markedly increased as compared with the exifone bulk substance.

In view of the results of the various tests mentioned above, it is apparent that, in the pharmaceutical composition of the present invention which comprises a physical mixture comprising exifone and a water-soluble cellulose derivative, both the drawback of exifone, namely, its being sparingly soluble in water, and the low absorbability into blood circulation upon oral administration, which is due to the sparing solubility of exifone, have been improved to a remarkable extent, and so the pharmaceutical composition of the present invention which comprises a physical mixture comprising exifone and a water-soluble cellulose derivative is very useful.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A pharmaceutical composition which comprises a physical mixture comprising exifone and a water-soluble cellulose derivative.

2. A pharmaceutical composition of claim 1, wherein the compounding ratio of exifone and the water-soluble cellulose derivative is 1:0.01 to 1:7 by weight.

3. A process for preparing a pharmaceutical composition comprising exifone and a cellulose derivative,

which comprises physical mixing exifone with a water-soluble cellulose derivative.

Claims for the following Contracting State : ES

1. A process for preparing a pharmaceutical composition comprising exifone and a cellulose derivative, which comprises physical mixing exifone with a water-soluble cellulose derivative.

2. Process according to claim 1, which comprises physical mixing exifone with a cellulose derivative in a compounding ratio from 1:0.01 to 1:7 by weight.

Patentansprüche
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Eine pharmazeutische Zusammensetzung, die eine physikalische Mischung, umfassend Exifone und ein wasserlösliches Cellulose-Derivat, umfasst.

2. Eine pharmazeutische Zusammensetzung aus Anspruch 1, worin das Mischungsverhältnis von Exifone und dem wasserlöstichen Cellulose-Derivat 1:0.01 bis 1:7 Gew.-Anteile beträgt.

3. Ein Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, umfassend Exifone und ein Cellulose-Derivat, das physikalisches Mischen von Exifone mit einem wasserlöslichen Cellulose-Derivat umfasst.

Patentansprüche für folgenden Vertragsstaat : ES

1. Ein Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, umfassend Exifone und ein Cellulose-Derivat, das physikalisches Mischen von Exifone mit einem wasserlöslichen Cellulose-Derivat umfasst.

2. Verfahren nach Anspruch 1, das physikalisches Mischen von Exifone mit einem Cellulose-Derivat in einem Mischungsverhältnis von 1:0.01 bis 1:7 Gew.-Anteilen umfasst.

Revendications
Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composition pharmaceutique comportant un mélange physique de l'exifone et un dérivé de la cellulose soluble dans l'eau.

2. Composition pharmaceutique selon la revendication 1 dans laquelle le rapport composant de l'exifone et du dérivé de la cellulose soluble dans l'eau est entre 1:0,01 à 1:7 en poids.

3. Procédé pour réparer une composition pharmaceutique comportant de l'exifone et un dérivé de la cellulose, qui comporte mélangé physiquement de l'exifone avec un dérivé de la cellulose soluble dans l'eau.

Revendications pour l'Etat contractant suivant : ES

1. Procédé pour la préparation d'une composition pharmaceutique comportant de l'exifone et un dérivé de la cellulose, qui comporte mélangé physiquement de l'exifone avec un dérivé de la cellulose soluble dans l'eau.

2. Procédé selon la revendication 1, comportant mélangé physiquement de l'exifone avec un dérivé de la cellulose dans un rapport composant de 1:0,01 à 1:7 en poids.